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Case Report
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Severe Worsening Axonal Neuropathy in Waldenstrom's Macroglobulinemia: Benefit of Nerve Biopsy

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Abstract

Background and Aims: Waldenström's Macroglobulinemia (WM) associated neuropathy is frequent. However, it can have different etiologies leading to different treatments, which makes the diagnosis challenging for the clinician.

Methods: Case study.

Results: We report the case of a 71-year-old female who presented a severe painful sensory motor axonal neuropathy. She had an IgM lambda monoclonal gammopathy with bone marrow and pleura lymphoplasmocytic cell infiltration, in favor of WM. The neuropathy worsened despite two lines of hematologic treatment. Nerve biopsy showed diffuse infiltrates of B and T cells with a B cell amplification confirmed on polymerase chain reaction based clonality testing.

Interpretation: Nerve biopsy is a key tool in the diagnosis of WM associated axonal neuropathy, especially for tumoral nerve infiltration since other classical investigations are often negative. The pathogenesis of this infiltration is debated, but our data are in favor of a hematogenic invasion by tumoral cells. Neuropathy secondary to tumoral nerve invasion may worsen in spite of good hematological response to treatment.

Keywords: EMG; Hematologic; Peripheral neuropathy; Nerve tumor; Biopsy

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Introduction

Waldenström's Macroglobulinemia (WM) is a distinct B-cell lymphoproliferative disorder characterized by IgM monoclonal gammopathy and bone marrow infiltration by lymphoplasmacytic cells [1]. WM associated neuropathy can be observed in around 40% of cases [3]. Although anti-MAG neuropathy is the most frequently described form, axonal neuropathy is common and has various etiologies. We report the case of a patient with severe sensory motor neuropathy that worsened despite treatment of WM, and that illustrates the diagnostic challenge of this situation.

Case Presentation

A 71-year-old female was admitted to our department in December 2018. Over the past two years, she had presented painful sensory disorders in her feet—progressively extending to the whole leg—and subsequent distal motor weakness. Concomitant 10 kg weight loss prompted systemic investigations in May 2018 that revealed an IgM monoclonal gammopathy with excess lambda free light chains at 200 mg/L. Lymphoplasmacytic cell infiltration into the bone marrow and pleura confirmed the diagnosis of WM with pleural localization and MYD88 mutation. Treatment with rituximab, dexamethasone and cyclophosphamide was initiated then switched to rituximab and bendamustine in October 2018 because of neurological worsening. Despite the decrease in lambda free light chains to 72 mg/L and regression of the pleural mass, sensory disorders extended to both hands and motor weakness reached the proximal part of the lower limbs. Electrophysiological studies revealed a severe progressive asymmetrical sensory motor axonal neuropathy. Complete laboratory tests were performed: Anti-MAG, anti-gangliosides and anti-neuronal antibodies were negative. The patient was positive for type 1 cryoglobulinemia with no evidence of complement

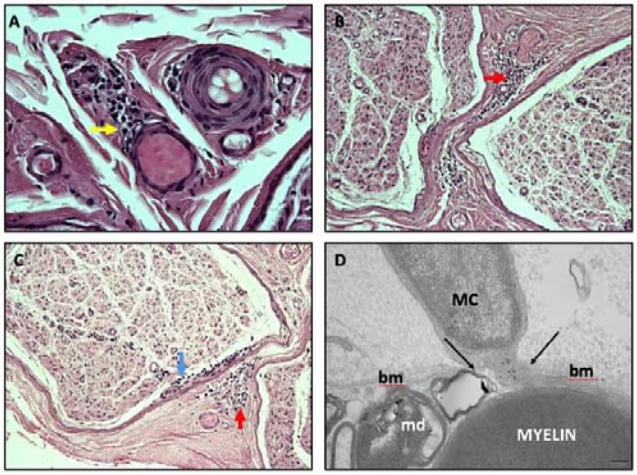

Figure 1: Superficial peroneal sensory nerve biopsy. (A-C): Optical microscopy with hematoxylin and eosin staining showing perivascular (A, yellow arrow), perineural (B, C, red arrow), and endoneural (C, blue arrow) infiltration by lymphoid mononuclear cells, without cytomorphological abnormalities. Absence of vessel wall breakage or occlusion of the vessel lumen is not in favor of vasculitis (A). Lymphoid cells reach the endoneurium by diffusing from the vessel through the perineurium and across the blood-nerve barrier (B,C). (D): Electron microscopy showing aggression of a Schwann cell nerve by a Mononuclear Cell (MC) which destroys the basal membrane (bm) and penetrates in the Schwann cell cytoplasm (between the black arrows); md: myelin debris.

consumption. Cerebrospinal Fluid (CSF) analysis was normal and included immunophenotyping and search for clonality. Salivary gland biopsy showed few amyloid deposits that were too small to be typed. Biopsy of abdominal subcutaneous fatty tissue was normal. Nerve Biopsy (NB) was subsequently performed. Nerve fragments were embedded in paraffin for staining, cut in transverse semi-thin and ultra-thin sections for optical and electron microscopy, and frozen for molecular biology. Congo red staining was negative. NB revealed severe axonal loss and nerve degeneration as well as perivascular, perineural and endoneural infiltrates of small mononuclear cells (Figure 1), identified as B and T cells by anti-CD20 and anti-CD3 staining, respectively. Polymerase chain reaction (PCR)-based clonality testing showed monoclonal B cell amplification.

Discussion

This observation demonstrates the relevance of NB in WM-related axonal neuropathy. Once electrophysiological studies and blood tests had ruled out a demyelinating process such as anti-MAG neuropathy, further investigations focused on mechanisms of axonal neuropathy such as amyloidosis, endoneural deposits of immunoglobulin, vasculitis or tumoral infiltration. Although salivary gland biopsy was suggestive of amyloidosis, NB showed no deposits stained by Congo red coloration or detectable in electron microscopy. There were no deposits of immunoglobulin in electron microscopy. The absence of cytomorphological abnormalities of cell infiltrates associated with positivity for type 1 cryoglobulinemia could be evocative of vasculitis but the preservation of the vessel wall ruled out this hypothesis [1,2]. Ultimately, clonality assessment by PCR was the key test to distinguish tumor lymphoproliferation from nonspecific reactive cell infiltrates. Tumoral nerve infiltration in WM is rarely described [3] and probably under estimated because explorations such as MRI, PET scans and CSF analysis can be negative [4]. In a retrospective study of 40 patients with WM-related neuropathy, 2 out of 25 patients with an axonal neuropathy had tumoral nerve infiltration [5]. In a more recent article, of 15 patients with neurolymphomatosis diagnosed with PCR analysis on NB, only one had WM [6]. Several mechanisms are suspected [7]: Contiguous nerve invasion, meningeal invasion, or hematogenous metastasis, but the exact pathogenesis remains unclear. Our images support the theory of a hematogenic invasion by tumoral cells, illustrating not only their accumulation in perivascular spaces as described in previous studies, but also their diffusion from the vessel to the endoneurium through the blood-nerve barrier and their aggressivity towards the nerve structure. Furthermore, this case highlights the existence of a dissociation between neurological and hematological responses to treatment in WM, in the same manner as there is no correlation between the severity of the hemopathy and the occurrence of a neuropathy [2]. Indeed, the neuropathy worsened despite the rise in IgM lambda, and the use of chemotherapy capable of crossing the blood-nerve barrier. This dissociation raises questions about the management of WM, and in particular how and when to evaluate treatment response or to conclude in treatment failure.

Severe progressive axonal neuropathy in WM despite hematological response to treatment may be evocative of tumoral nerve invasion. NB is a useful tool to confirm this diagnosis but also to improve our insight into the pathogenesis.

References

1. Owen RG, Treon SP, Al-Katib A. Clinicopathological definition of Waldenstrom's macroglobulinemia: Consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. Semin Oncol. 2003;30:110-5.
2. Levine T, Pestronk A, Florence J. Peripheral neuropathies in Waldenstrom's macroglobulinaemia. J Neurol Neurosurg Psychiatry. 2006;77:224-8.
3. Vital C, Vallat JM, Deminiere C, Loubet A, Leboutet MJ. Peripheral nerve damage during multiple myeloma and Waldenstrom's macroglobulinemia: An ultra-structural and immunopathologic study. Cancer. 1982;50:1491-7.
4. Baehring JM, Batchelor TT. Diagnosis and management of neurolymphomatosis. Cancer J. 2012;18:463-8.
5. Viala K, Stojkovic T, Doncker AV. Heterogeneous spectrum of neuropathies in Waldenstrom's macroglobulinemia: A diagnostic strategy to optimize their management. J Peripher Nerv Syst. 2012;17:90-101.
6. Duchesne M, Roussellet O, Maisonobe T. Pathology of nerve biopsy and diagnostic yield of PCR-based clonality testing in neurolymphomatosis. J Neuropathol Exp Neurol. 2018;77:769-81.
7. Briani C, Visentin A, Campagnolo M. Peripheral nervous system involvement in lymphomas. J Peripher Nerv Syst. 2019;24:5-18.